Department of Health and Human Services
National Institutes of Health
National Center for Advancing Translational Sciences Advisory Council
and
Cures Acceleration Network Review Board
Minutes of Virtual Joint Meeting
January 10, 2019

The National Center for Advancing Translational Sciences (NCATS) Advisory Council and the Cures Acceleration Network (CAN) Review Board held a joint meeting in open session on January 10, 2019, convening at 11:00 a.m. ET, via WebEx and in Conference Room 987/989, Democracy 1 Building, at the National Institutes of Health (NIH). Christopher P. Austin, M.D., NCATS Advisory Council chair, and G. Lynn Marks, M.D., CAN Review Board chair, led the meeting. In accordance with Public Law 92-463, the session was open to the public.

Following the joint meeting, the NCATS Advisory Council met in closed session for the review and consideration of grant applications.

NCATS ADVISORY COUNCIL MEMBERS **PRESENT**

Chair

Christopher P. Austin, M.D., Director, NCATS

Executive Secretary

Anna L. Ramsey-Ewing, Ph.D., Director, Office of Grants Management and Scientific Review, NCATS

Council Members

Ronald J. Bartek, M.A.
Daniel Hartman, M.D.
Katharine Ku, M.S.
Richard E. Kuntz, M.D., M.Sc.
Geoffrey Shiu Fei Ling, M.D., Ph.D.
Brad Margus, M.B.A.
G. Lynn Marks, M.D.
Kalpana Merchant, Ph.D.
Megan O'Boyle
Alan D. Palkowitz, Ph.D.
Harry P. Selker, M.D., M.S.P.H.
Anantha Shekhar, M.D., Ph.D.

Representative Members

None present

Ex Officio Members

Rachel Ramoni, D.M.D., Sc.D., Chief Research and Development Officer (CRADO), Veterans Health Administration, U.S. Department of Veterans Affairs (VA Research)

CAN REVIEW BOARD MEMBERS **PRESENT**

Chair

G. Lynn Marks, M.D., Senior Research and Development (R&D) Advisor, Biomedical Advanced Research and Development Authority (BARDA), Office of the Assistant Secretary for

Preparedness and Response (ASPR), U.S. Department of Health and Human Services (HHS); and Chair, CAN Review Board

Vice Chair

Ronald J. Bartek, M.A., Co-Founder and Founding President, Friedreich's Ataxia Research Alliance (FARA)

Executive Secretary

Anna L. Ramsey-Ewing, Ph.D., Director, Office of Grants Management and Scientific Review, NCATS

Board Members

Daniel Hartman, M.D.
Katharine Ku, M.S.
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Anantha Shekhar, M.D., Ph.D.

Representative Members

None present

Ex Officio Members

Rachel Ramoni, D.M.D., Sc.D., Chief Research and Development Officer (CRADO), Veterans Health Administration, U.S. Department of Veterans Affairs (VA Research)
Frank F. Weichold, M.D., Ph.D., Director, Critical Path and Regulatory Science Initiatives, Office of Regulatory Science and Innovation, Office of the Chief Scientist, Office of the Commissioner, Food and Drug Administration (FDA)

OTHERS PRESENT

None

NCATS leadership and staff

I. CALL TO ORDER AND OPENING REMARKS, OPEN SESSION: Christopher P. Austin, M.D., Director, NCATS, and Chair, NCATS Advisory Council; G. Lynn Marks, M.D., Senior R&D Advisor, BARDA, ASPR/HHS, and Chair, CAN Review Board

Christopher P. Austin, M.D., and G. Lynn Marks, M.D., called the meeting to order at 11:06 a.m. ET. Dr. Austin welcomed members and guests to the 20th meeting of the NCATS Advisory Council and the 26th meeting of the CAN Review Board. Dr. Marks extended a welcome to everyone on behalf of the CAN Review Board, and Dr. Austin introduced the members of the council and board and previewed the meeting agenda.

Dr. Austin reminded attendees that the open session was being webcast and also explained this would be the first virtual joint meeting of the advisory groups. He acknowledged that teams work best when the members are in the same room; for this reason, virtual conferencing probably would be reserved for January meetings. He asked members to provide feedback about the virtual meeting format to help NCATS understand what works well for them and for NCATS and would best serve the missions of NCATS and the advisory groups.

II. APPROVAL OF MINUTES AND STANDARD OPERATING PROCEDURES: Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, NCATS Advisory Council and CAN Review Board

Anna L. Ramsey-Ewing, Ph.D., announced that the September 2018 minutes, the 2019 council operating procedures, and a briefing on NCATS' 2018 scientific activities were available in the electronic council book. Members unanimously approved the minutes and procedures.

III. DATES OF FUTURE MEETINGS: Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, NCATS Advisory Council and CAN Review Board

Anna L. Ramsey-Ewing, Ph.D., confirmed the schedule for the meetings of the NCATS Advisory Council and CAN Review Board in 2019 and 2020:

- May 16, 2019
- September 19, 2019
- December 13, 2019 (virtual meeting; CAN Review Board only)
- January 16, 2020 (likely a virtual meeting)
- May 14, 2020
- September 17, 2020
- December 11, 2020 (virtual meeting; CAN Review Board only)

IV. STAFFING ANNOUNCEMENTS: Michael Kurilla, M.D., Ph.D., Director, Division of Clinical Innovation, NCATS; Penny Burgoon, Ph.D., Director, Office of Policy, Communications and Education, NCATS

Michael Kurilla, M.D., Ph.D., introduced Soju Chang, M.D., M.P.H., who is responsible for managing the Clinical and Translational Science Awards (CTSA) Program hubs. Dr. Chang came to NCATS from his previous position as a program officer with the National Institute of Allergy and Infectious Diseases (NIAID). In his role with the CTSA Program, Dr. Chang serves as a subject matter expert on human subject research and also is a valued member of the Trial Innovation Network team.

Also new to NCATS is Xinzhi Zhang, M.D., Ph.D., who is involved with the CTSA Program hubs and education teams. Before joining NCATS, Dr. Zhang was with the National Institute on Minority Health and Health Disparities, working in the areas of community health and population sciences. Dr. Zhang will take the lead on the Center's new focus on health disparities and rural health across the CTSA Program and help NCATS engage with other federal partners working in this space.

Penny Burgoon, Ph.D., announced that Cindy McConnell, the chief of NCATS' Communications Branch, will be leaving NCATS to join the National Institute on Aging (NIA) as director of communications and public liaison. Bobbi Gardner is stepping in as the acting chief of communications for the time being.

V. DIRECTOR'S REPORT: Christopher P. Austin, M.D., Director, NCATS

Dr. Austin began by thanking two outgoing members of the NCATS Advisory Council and CAN Review Board: Harry Selker, M.D., M.S.P.H., and Anantha Shekhar, M.D., Ph.D., who have served NCATS' advisory groups in an exemplary manner for several years.

Dr. Austin announced that Joni Rutter, Ph.D., has been appointed deputy director of NCATS. Dr. Rutter's training was in human genetics, and her familiarity with opportunities in genomic medicine dovetails with NCATS' work in translational science, as does her background in pharmacology and precision medicine.

Dr. Rutter has been the director of scientific programs for the *All of Us* Research Program since its inception and previously served as director of the Division of Neuroscience and Behavior at the National Institute on Drug Abuse. She looks forward to advancing precision medicine at NCATS.

The Year in Review: Fiscal Year 2018

Dr. Austin provided a retrospective on uses of NCATS' funds during fiscal year (FY) 2018. He reported that NCATS' FY 2018 budget was $742 million, near the median for all NIH Institutes and Centers (ICs). Dr. Austin added that this figure does not reflect $20.1 million transferred from the National Institute of Neurological Disorders and Stroke to NCATS for the NIH HEAL (Helping to End Addiction Long-term℠) Initiative, a trans-agency effort to speed scientific solutions to stem the national opioid public health crisis. Including this sum bumps up NCATS' total FY 2018 allocation to $760.7 million.

About 70 percent of NCATS' budget goes to the Division of Clinical Innovation's (DCI) clinical research programs, mainly the CTSA Program. The Division of Pre-Clinical Innovation (DPI) receives about 10 percent of the budget, and CAN a slightly smaller proportion. The remaining funds support rare diseases research and a variety of other programs.

Dr. Austin presented a chart showing that NCATS' budget has increased every year since 2013.

The Division of Clinical Innovation (DCI)

The CTSA Program is the largest single program at NIH, and a detailed table of its funded activities is available online. Dr. Austin provided a list of the new hub awards issued last year.

In addition, CTSA Program hubs may apply for administrative supplements to take advantage of new opportunities. In FY 2018, seven supplements were awarded for a total of $3.4 million to enhance network capacity by facilitating the sharing of information and innovations among the hubs. According to Dr. Austin, the 2018 supplements supported adaptation of innovations so they can work across the ecosystem of translational science.

With regard to the CCIAs, Dr. Austin noted that the funding mechanism supports new collaborations among two or more CTSA Program hubs or with outside entities. At present CCIAs support collaborations among 36 different institutions. The 2018 CCIAs focused on topics to engage patients and communities, promote integration of special and underserved populations into research, innovate processes to increase quality and translational research, and support informatics resources.

In the spring of FY 2018, NCATS received a sizable increase in its appropriation with only a short time to obligate it. Major effort over the summer of 2018 allowed NCATS to allocate $14 million to a variety of priority research areas, including informatics, addressing the opioid crisis, and promoting diversity and re-entry of scientists into biomedical and behavioral research careers. Ultimately, 27 awards, including 15 administrative supplements and 12 CTSA Program Collaborative Innovation Awards (CCIAs), were made to 24 CTSA Program hubs.

The Division of Pre-Clinical Innovation (DPI)

Staffed with over 200 scientists and trainees who are expert in preclinical translation from target validation to IND-enabling studies, DPI is the intramural part of NCATS, Dr. Austin said. Every project is collaborative, and partners include academic investigators, companies, and foundations. A total of 183 projects were in progress across the Division in 2018, each focusing on developing the science needed to overcome a translational roadblock for a particular target or disease intervention, while at the same time establishing a generally-useful paradigm or technology that will make future projects more efficient and/or successful.

In FY 2018, DPI staff published 90 articles in peer-reviewed journals. Dr. Austin highlighted a few high-impact papers by DPI scientists and called attention to the number of authors on these articles as evidence that the research has been highly collaborative and productive.

Dr. Austin described two DPI projects in detail. The first, Canvass, is a crowd-sourced natural product screening library for exploring biological space. All the data go into an open-source database to ensure they remain publicly available. A second project, the NCATS Tissue Bioprinting Laboratory, hit its stride in 2018. The laboratory is creating morphologically and pharmacologically validated biofabricated human 3-D tissue models in microwell plates for drug screening. The models represent retina, skin, neurovascular systems, and peritoneum/omentum in both normal and disease states.

DPI's Therapeutics Development Branch includes the Therapeutics for Rare and Neglected Diseases and the Bridging Interventional Development Gaps programs. In 2018, two collaborative investigational new drug (IND) projects were initiated, one for pulmonary hypertension and the other for fragile X syndrome. Additionally, 15 HEAL proposals are under consideration for IND-enabling studies.

The Office of Rare Diseases Research (ORDR)

Dr. Austin spoke about the Office of Rare Diseases Research's (ORDR) highly catalytic conference grants funded through the R13 mechanism. The grant program brings together rare disease experts and patient and disease advocates by funding conferences entirely or jointly with other ICs. ORDR issued 31 such grants in 2018 at a total cost of $350,000.

Dr. Austin highlighted a few new and ongoing projects funded by ORDR's Bench-to-Bedside grants. One project, co-funded with NIAID, is a study of targeted CRISPR-mediated hematopoietic stem cell gene therapy for X-linked severe combined immunodeficiency. Another project, co-funded with the National Heart, Lung, and Blood Institute, focuses on gene therapies to cure sickle cell disease.

Dr. Austin presented the topics covered during an August 2018 breakthrough conference with the U.S. Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research on the promise of gene therapy for treating rare diseases.

The NCATS Rare Diseases Are Not Rare! Challenge aims to redefine rare diseases as a public health problem. According to Dr. Austin, rare diseases affect 8 percent of the population, representing a prevalence similar to that of type 2 diabetes. The challenge attracted 44 entries, including videos, songs, drawings and quizzes; winners will be featured during Rare Disease Day at NIH on February 28, 2019.

The HEAL Initiative

Within the HEAL Initiative, NCATS is leading a preclinical program to develop human cell-based platforms for developing and testing new treatments for pain, opioid addiction and overdose, and a clinical program to create a Pain Effectiveness Network based on the CTSA program.

Dr. Austin remarked on A Specialized Platform for Innovative Research Exploration (ASPIRE), which grew out of a concept advanced by the CAN Review Board in 2017. Through ASPIRE, NCATS aims to transform chemistry from an artisanal craft to a predictive data-driven science. By addressing barriers such as lack of standardization, low reproducibility and inability to predict biological activities of new chemical structures, ASPIRE aims to catalyze the efficient creation of novel, safe and effective treatments.

In late 2018, ASPIRE released a set of challenges through the NIH HEAL Initiative. Submissions are due by May 31, 2019, and winners will be announced in August 2019. The goal of the inaugural ASPIRE Design Challenges is to design innovative and catalytic approaches toward solving the opioid crisis. Dr. Austin said that the challenge mechanism is new to NCATS, and has now been used twice: the Rare Diseases Are Not Rare! Challenge and ASPIRE Design Challenges.

CAN-Supported Activities

Among the other activities of CAN, the Tissue Chip Program was particularly productive in 2018, as reported by Dr. Austin:

- **Tissue Chips for Disease Modeling and Efficacy Testing:** Seventeen cooperative agreement awards were made by NCATS and other ICs.
- **NextGen Testing Centers and Microphysiological Systems (MPS) Database Center:** NCATS made two awards for testing centers and one for database support for the Tissue Chip program.
- **Tissue Chips in Space:** Nine awards were made for transporting tissue chips to the International Space Station. The National Aeronautics and Space Administration (NASA) contributed $1.2 million to the initiative, and the Center for the Advancement of Science in Space (CASIS) provides $8 million in in-kind support for each launch. The next launch, scheduled for March 2019, will carry chips into space for studying muscle wasting, gut inflammation and cardiac dysfunction.
- **HEAL administrative supplement awards (non-CAN dollars):** Nine awards ($2.5 million) are supporting development of tissue chip models of pain and addiction.

The Small Business Innovation Research and Small Business Technology Transfer Programs

Dr. Austin reported that Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) contract awards represent about 3 percent of NCATS' budget. However, there has been a large increase in the number of applications over the years. In 2018, 59 percent of NCATS' SBIR/STTR funding supported the development of tools for drug discovery and development.

Dr. Austin mentioned that NCATS provided early funding to Recursion Pharmaceuticals, which has developed a novel approach for rapid multiplex testing of drugs in human cell types. Since receiving the NCATS SBIR award, Recursion has attracted more than $100 million in investments and established strategic partnerships with Sanofi and Takeda. In 2018, the company launched its first clinical program.

Dr. Austin also updated the group on IonField Systems, which used NCATS SBIR funding to develop and commercialize an automated plate cleaner, saving hundreds of thousands of research dollars and dramatically reducing environmental plastic waste. In 2018, IonField Systems and AstraZeneca announced the successful completion of the PlasmaKnife Microplate Cleaning System beta test and the first installation of a commercial release of the technology.

Looking Ahead

Dr. Austin announced that HHS is continuing to operate under the budget signed into law in September 2018 (P.L. 115-245). For FY 2019, NIH appropriations increased by $2 billion over FY 2018, for a total of $39.084 billion, and NCATS' FY 2019 budget is $806.4 million.

The FY 2020 budget process has already begun, with the president's budget expected on February 4 and congressional hearings to be scheduled in the spring. However, during the shutdown, many members of staff working on the budget had been furloughed.

Dr. Austin announced that NCATS will sponsor a February 2019 symposium on the opioid crisis and preclinical development of new therapeutics for addiction and pain. The event will be run by the DPI Assay Guidance Manual group.

Discussion

Mr. Bartek commented that ORDR's conference grant program is absolutely essential in establishing new disease groups and fostering collaboration. Moreover, given the modest sums of money involved, conference grants are as cost-effective as they are useful.

VI. CURES ACCELERATION NETWORK REVIEW BOARD UPDATE: Ronald J. Bartek, M.A., Co-Founder and Founding President, Friedreich's Ataxia Research Alliance, and Vice Chair, CAN Review Board; G. Lynn Marks, M.D., Senior R&D Advisor, Biomedical Advanced Research and Development Authority (BARDA), ASPR/HHS, Chair, CAN Review Board; and Christine Colvis, Ph.D., Director, Drug Development Partnership Programs, NCATS

Dr. Marks updated the Advisory Council on the outcomes of the CAN Review Board meeting held on December 14, 2018.

A Process for Advancing CAN Research Proposals

Dr. Marks and Mr. Bartek suggested a process whereby the CAN Review Board can develop and propose research concepts to the NCATS Advisory Council to consider for funding. Members of the CAN Review Board would come up with an idea, bring it to the CAN Review Board for discussion and refinement, and the board would then vote on whether to take it forward to the Advisory Council and NCATS. The idea is that having a process will allow the CAN Review Board to take active control over ideas it wishes to recommend for funding by NCATS. The process would proceed thus:

CAN RB Project Proposal → Focus Areas→Concepts→Solicitations→Awards→Solutions

Dr. Marks outlined the key principles and requirements for CAN activities:

- Focus on open, fair, transparent competition.
- Use appropriate expertise.
- Ensure objectivity and integrity throughout the process.
- Exercise ongoing safety, fiduciary, and other stewardship.

Although NCATS operates on an accelerated timeline, compression of that timeline must be limited to what is allowable or advisable.

Dr. Ramsey-Ewing presented a timeline for developing a typical NIH initiative, requiring about 28 months from inception to award. She then compared this timeline to the potential timeline for new CAN projects. During the meeting, the Advisory Council will vote on a CAN Review Board proposal on gene therapy and discuss a second proposal on drug repurposing. Awards for the first proposal could be made as soon as the summer of 2020 and, for the second proposal, the fall of 2020. It is possible that these timelines could be accelerated if the anticipated workshops are highly productive, and Dr. Marks added that it might be possible to divide up the projects and start some segments sooner.

CAN Project Proposal 1: Gene Therapy

Mr. Bartek said that gene therapy is an area in which the CAN Review Board and NCATS can have a great and immediate positive impact by eliminating barriers. Hundreds of gene therapy trials are underway, but all gene therapy programs face common barriers that cause multiyear delays and drive costs up. These impediments will only get worse if it is up to individual programs to dismantle the barriers. Mr. Bartek reported that six key issue areas have emerged:

- **The need to develop standardized predictive measures/assays of neutralizing or particle-clearing antibodies to major serotypes:** All gene therapy programs struggle to determine which patients to recruit based on prior exposure to the vector and immune response anticipated; in some cases, immune response is mounted to the gene product itself.
- **Immune response, suppression, transduction attenuation and redosing:** All programs face questions such as how to predict immune response and how to suppress it, how to compare response across studies by designing a platform for uniform sample collection and testing

following treatment, and how to determine whether subsequent dosing with the same or a different vector is feasible and advisable.

- **Assays for potency, biodistribution and filled particle quantitation:** Gene therapy programs need ways to determine which tissues the target protein penetrates and to what extent it is active there. Could standard biodistribution assays obviate the need to repeat biodistribution studies when the same capsid is used to deliver different transgenes?
- **Manufacturing:** As there are very few manufacturers of gene therapy compounds, antiquated analytical and manufacturing technologies are in use, extremely long queues cause horrendous delays in development, capital costs remain very high and prices exorbitant, large volumes of product are required for clinical trials and orders of magnitude larger volumes needed for treatment. Solutions could include development or provision of more advanced technologies, such as higher-yield particle expression systems and quality control assays for host cell impurities.
- **Scientific tools to inform clinical trial design, selection of initial subjects and dosing levels:** Given the likelihood that gene therapy will be a one-time or limited-time treatment, programs need to establish the first, therapeutic dose. Regarding enrollment criteria, should researchers adjust standard paradigms in determining age and progression levels of first trial subjects? Would it be necessary to establish safety profiles in older patients? How could younger pediatric patients enroll in early trials?
- **Gene therapy programs using nonviral vectors:** A similar list of issues must be considered.

Mr. Bartek observed that the solutions to these challenges lie at the center of the CAN Review Board mandate: to accelerate the development of high-need cures. He underscored the importance of NIH being involved in solving these problems, as NIH can require that solutions be universally shared.

A series of workshops and other stakeholder engagement events organized by NCATS and the CAN Review Board would help define the candidate issues. Dr. Marks said that the first workshop would probably be quite general in terms of content, and subsequent workshops would focus on a couple of issues at a time.

Dr. Bartek concluded by saying that the CAN Review Board recommends this program of research to NCATS because the Center, in collaboration with the CAN Review Board, is uniquely well equipped to advance the translational sciences needed to resolve all six barriers to gene therapy.

Discussion

Dr. Selker expressed his support for the research proposal. Daniel Hartman, M.D., was also in favor of advancing the gene therapy program and asked about the possible need for common data standards, which would serve all programs developing gene therapies for similar conditions to share data across groups and studies. Mr. Bartek noted that designing a platform would absolutely require common data elements and recommended adding language addressing this requirement.

Frank F. Weichold, M.D., Ph.D., emphasized the importance of data interoperability and defined metadata standards for laboratory, clinical and preclinical data to understand their provenance and authenticity. He asked about considering precertification of gene therapy programs and manufacturers concerning qualifications, competence and expertise in order to support a streamlined FDA review process of devices and cell products. Mr. Bartek said that this issue has not been specifically addressed, and since the government shutdown, it has been challenging to work with FDA colleagues. However, the FDA would clearly be essential to this entire effort, and Dr. Weichold expressed a willingness to push for any needed legislative changes to expedite FDA reviews to better serve patients and innovators.

Mr. Bartek added that the FDA's draft guidance on gene therapy in rare diseases has been instrumental in shaping these issues and leading the CAN Review Board toward solutions. When the final guidance comes out, there will be a good foundation and context for embracing legislative solutions.

Rachel Ramoni, D.M.D., Sc.D., asked about availability of existing data sets cataloguing prior gene therapy approaches. What are the data needs of people working on gene therapy for a certain condition? According to Philip John (P.J.) Brooks, Ph.D., the NIH Genetic Modification Clinical Research Information System (GeMCRIS®), which had been supported by the NIH Office of Biotechnology Assessment, is a voluntary catalog of gene therapy efforts. The problem is that companies do not deposit information in it. That is why this proposed effort is so important: everyone would have access to all the data. This might also be true for vectors.

Kalpana Merchant, Ph.D., remarked on the need to consider the tropism of capsid vectors for human brain cells. Screening in rodents does not reflect human tropism; one must use nonhuman primates. That is a major bottleneck for therapies targeting brain cells. Dr. Marks thought that this research barrier would be addressed during the series of workshops.

A motion was made and seconded to advance the gene therapy proposal. The motion passed unanimously.

CAN Project Proposal 2: Drug Repurposing

Christine M. Colvis, Ph.D., director, Drug Development Partnership Programs, NCATS, presented this proposal. Dr. Selker had raised the topic of drug repurposing during the CAN Review Board's December meeting, but NCATS staff had already been in involved in thinking about an approach to this issue and discussing it with the FDA. Dr. Colvis said that a group of CAN Review Board members developed a white paper providing additional background on this problem.

When a drug goes off patent and becomes available as a generic, it is possible to patent new uses of the drug, but obtaining marketing approval for the new indication (i.e., labeling change) requires a considerable investment in clinical trials to collect the evidence required by the FDA. With generic versions, the pricing cannot support this investment in trials regardless of how promising the drug might be for another condition. There is no path forward for repurposing generic drugs, and apart from NCATS, few resources exist to support drug repurposing.

The overall goal for this proposal is to plan a workshop to discuss incentives for development of low-cost, high-impact therapies. Among the topics for discussion at a workshop would be the following:

- What is working well, and what has been a barrier? Dr. Colvis recommended considering the Best Pharmaceuticals for Children Act and how it changed the landscape for pediatric indications.
- What are the top-priority drugs and indications in need of label updates?
- What sources of data (e.g., real-world evidence, Big Data) could be used, and what level of evidence would be needed to supplement or expand labeling?
- Who could be a regulatory sponsor for these types of development efforts?
- What incentives would encourage private sector participation?

Dr. Colvis said that the workshop should include participants from many segments of the ecosystem, including representatives from other ICs, the Centers for Medicare & Medicaid Services, insurers, health economists, and patients. She recommended working with the FDA to identify the level of evidence necessary to support a label change.

Discussion

Dr. Selker agreed on the importance of involving all stakeholders. NCATS could serve as the convening organization. This type of research fits the mission of both CAN and NCATS, because the challenge exists at the interface of NIH and industry. Drug prices are a national concern, and increasing the availability of low-cost generic drugs for new indications would be one way to help cut drug costs. This project would entail minimal risk, but the potential rewards would be great and have global implications.

Dr. Ramoni listed several ideas for ensuring that the workshop, as well as the overall effort, would be successful: First, invite the right people to the workshop. Second, be mindful that legislative action may be needed. The VA has been successful in getting members of Congress and their staff interested in various initiatives. Third, the project would require a robust communication effort to make others aware of what is happening. Fourth, the project would need a strategic component because outcomes would require viable business models for repurposing, and repurposing would challenge the existing paradigm built upon the role of pharmaceutical companies. Dr. Ramoni expressed an interest in helping with the drug repurposing initiative.

Dr. Weichold agreed on the importance of developing a business model for drug repurposing and having access to data. The FDA wholly supports evidence-based medicine, but gaining unfettered access to complex data sets is a ubiquitous challenge. The economic question embedded in drug repurposing will have to be answered with evidence. Dr. Weichold highlighted the critical foundations for drug repurposing, namely leveraging of real-world evidence and liberating health data to address the lack of clinical trial data. The workshop will be an opportunity to emphasize these ideas and gain access to data experts who can clarify what evidence would be needed to support new indications.

Alan D. Palkowitz, Ph.D., reiterated the importance and timeliness of this topic, given the factors shared. From the angle of the pharmaceutical industry, it might be important to people representing those who would be in a position to craft legislation around protecting intellectual property of companies. It would be helpful to include that perspective in the dialogue and give parties a tie-back to the challenges of the existing industry model.

Geoffrey Shiu Fei Ling, M.D., Ph.D., supported the proposal, saying that it would give NCATS an opportunity to demonstrate great leadership. He recommended involving additional stakeholders, including private equity investors, venture capitalists and foundations. Dr. Ling suggested discussing where the products would be manufactured as a way of garnering support for the effort.

Dr. Shekhar brought up another issue: Repurposing off-patent drugs would change the current paradigm of the FDA and the pharmaceutical industry being the intermediaries of access to novel medications. He suggested engaging with the Center for Medicare & Medicaid Innovation as a possible advocate, as the Innovation Center has certain authorities, and proposed including the chief innovation officer in the discussion.

A meeting participant said uncertainties around Prescription Drug User Fee Act (PDUFA) fees are significant barriers for generic drug manufacturers.

Dr. Hartman said that generic drug indications are a frequent issue in global health. There are financial incentives and policy guidelines for label changes. However, drugs are not used just for label indications, and it is worthwhile to consider the policies and guidance put out by societies and institutions.

Dr. Weichold asked about amending the CAN Review Board process to allow email voting in order to expedite decisions on research proposals. Dr. Marks opposed the suggestion, saying it is important to clarity, buy-in and agreement across the CAN Review Board about the recommendations it brings forward to NCATS. Regarding this particular proposal, he said the team will consider the points discussed at this

meeting and then refine the proposal further to identify stakeholders and clarify the Review Board's research proposal for NCATS. Dr. Weichold agreed the time could be used productively.

Mr. Bartek said that FARA, on its own, has not been able to assemble a feasible approach to drug repurposing. NCATS may be the right organization to get stakeholders together, including patients and advocates, to come up with a solution. Patients are very interested in effective but less costly treatments. Megan O'Boyle said new uses of existing drugs could improve patients' lives and mentioned the Orphan Drug Act, which helps promote drug development for rare diseases. She predicted that many policy issues will crop up. Brad Margus, M.B.A., said that as a patient advocate, he fully supports convening workshops to further this research proposal.

Katharine Ku, M.S., said that in academic institutions, if faculty are interested in pursuing new indications for a drug, the institution's technology transfer offices are frequently reluctant to proceed.

Dr. Ramoni asked whether the focus of this research proposal is exclusively on off-patent drugs. There might be off-label uses of drugs within the patent period that could help in rare diseases. Dr. Selker said that companies can take advantage of exclusivity initiatives through the FDA to add indications, but it is not clear that this mechanism is being applied efficiently across the breadth of rare diseases. Mr. Bartek said that this issue would be clarified before bringing the proposal for a vote.

Next Steps

Mr. Bartek said that the team working on this proposal will work with Dr. Colvis to revise the proposal.

Dr. Marks said that sufficient interest exists for the CAN Review Board to proceed with this proposal. A vote will be taken at the May meeting.

VII. TISSUE CHIP PROGRAM UPDATE: Danilo A. Tagle, Ph.D., M.S., Associate Director for Special Initiatives, Office of the Director, NCATS

Danilo A. Tagle, Ph.D., M.S., focused on commercialization of tissue chip technology and reviewed the background of the Tissue Chip program. The goal of the program is to disseminate the technology and create an ecosystem for its deployment. He noted that NIH has been investing in the Tissue Chip program since 2012. Until 2017 the focus was on developing the platforms, but over the past three years it has shifted to functional validation of the chips with a training set of compounds and assessing multi-organ integration. The tissue chip technology has been the topic of more than 500 articles published in high-profile journals.

Regarding the question of whether the organs-on-chips can predict toxicity, Dr. Tagle said the answer is yes.

NCATS serves a leadership role for the Tissue Chip Consortium, and the Center has partnerships with the Defense Advanced Research Projects Agency (DARPA), the FDA, NASA, the Biomedical Advanced Research and Development Authority (BARDA), nonprofit organizations and professional societies. NCATS has also established Tissue Chip Testing Centers (TCTCs) and the Tissue Chip Data Center.

Dissemination of the Technology

Now the program aims to get the technology into the hands of drug developers and stakeholders in the field. Dr. Tagle enumerated several key elements in disseminating the new technology, including the need for early engagement with end users and ensuring the technology meets market needs in drug discovery. Right now the control systems are more complex than the chips themselves, and the tissue chips will have to be transformed to turnkey technology.

Some startups and spinoffs have grown out of academic centers, especially through NCATS' SBIR program. Pharmaceutical companies and the FDA are interested in using organ chips in drug testing and regulatory

decision making, and Johnson & Johnson and Merck have partnered with Emulate, Inc., to develop applications for organs on chips.

IQ Microphysiological Systems is an entity created by the pharmaceutical industry. It consists of a multidisciplinary team of pharmaceutical scientists sharing information among IQ member companies and also provides a forum for engaging with regulatory authorities.

Building Confidence in the Technology

Dr. Tagle explained the Tissue Chip Validation Framework, which aims to answer questions such as whether the chips mimic organ function and structure and respond appropriately when exposed to various conditions. The TCTCs are carrying out the analytical stage, testing the chips with a validation set of compounds, biomarkers and assays. The next stage is the industrial stage, in which companies adopt and commercialize the technology.

According to Dr. Tagle, a program started in 2018 for using the chips in disease modeling and efficacy testing. Two-thirds of the funding for this program came from other ICs, a demonstration of successful leveraging of NCATS dollars to stimulate their investment.

Of the Tissue Chips in Space program, Dr. Tagle said the goal is studying physiological changes, including aging, under prolonged microgravity. Astronauts experience significant health changes during spaceflight, including increasing renal stone risk and declining immunity, which seem to represent accelerated aging, but they return to normal physiology once back on Earth. NCATS' Tissue Chips in Space awards enable biotechnology firms to examine immunosenescence, osteoporosis, kidney stone formation, the blood-brain barrier integrity and other changes affected by spaceflight. NCATS is also interested in collaboration with NASA engineers and payload developers to produce innovations and improvements, which will involve incubators, microscopes, microfluidic pumps and other instrumentation miniaturized and converted to turnkey technology for space deployment.

The Future of Tissue Chips

Dr. Tagle spoke of plans for conducting clinical trials on chips. This concept was cleared at the most recent Advisory Council meeting, and the initiative is being developed for FY 2020.

Discussion

A meeting participant asked about the possibility of using tissue chips to address issues surrounding gene therapy (for example, identifying tissues that might respond to therapy). Dr. Tagle said NCATS and the FDA discussed using tissue chips as model systems to test biologics, including gene therapy with CRISPR products, as they cannot be tested in animal systems. A participant then proposed including relevant tissue chip staff in the gene therapy workshops.

Dr. Palkowitz said it will be interesting to see how this technology affects discovery of new therapeutics and asked whether TCTCs might become fee-for-service providers for testing compounds. Dr. Tagle replied that part of the vision is a fee-for-service system whereby pharmaceutical companies could access expertise and chip technology for generating data to move a compound into development.

Dr. Ling applauded the cross-agency collaboration resulting in this technology. The program is highly synergistic in terms of its goals and end users from NIH and the Department of Defense, and is now transitioning into aerospace. He recommended involving even more agencies in the program.

Dr. Merchant asked if pharmaceutical firms are participating in the Tissue Chip Consortium. She observed that some companies using the tissue chip platform developed at one center have run into issues. Dr. Tagle said pharmaceutical companies are participating in the validation phase. All tissue chip data are housed and disseminated through a database, and stakeholders have access to varying tiers of data.

Dr. Ramoni asked about using the tissue chips to understand the effects of spaceflight. According to Dr. Tagle, Lucie Low, Ph.D., the NIH-NASA liaison point of contact, organized a workshop with NASA headquarters to discuss opportunities for studying longer spaceflights, such as the mission to Mars, but this initiative has been delayed by the government shutdown. Dr. Ramoni said the VA would be interested in learning more about this initiative, as the VA will provide care to astronauts as they transition to veteran status.

ACTION ITEM: Dr. Austin and Dr. Ramoni will discuss the possibility of offering a presentation by Dr. Low and Dr. Austin to VA officials and scientists.

ACTION ITEM: Dr. Tagle volunteered to distribute his slide deck to the members of the NCATS Advisory Council and the CAN Review Board.

VIII. CLEARANCE OF CONCEPT: SYNTHETIC TECHNOLOGIES FOR ADVANCEMENT OF RESEARCH AND THERAPEUTICS (START) — ENGINEERING THERAPEUTIC ENZYMES: Danilo A. Tagle, Ph.D., Associate Director for Special Initiatives, Office of the Director, NCATS

The council and board received a presentation on a new project NCATS is considering for funding. At the conclusion, members discussed the proposal and voted on whether to approve NCATS' moving forward with the initiative.

Dr. Tagle said there are hundreds of metabolic disorders for which there are no treatments. Enzyme replacement therapies (ERT) comprise the current standard of care, and patients could benefit if ERT cost less and were more effective in certain tissue types, treatments could cross the blood-brain barrier, and manufacturing processes were improved.

In this context, snthetic biology is the engineering of non-natural pathways in hosts to generate novel, therapeutically relevant compounds. Production of the compounds could be inducible, or the compound could be encapsulated in the body to meet biological demand.

The goal of this project would be to use synthetic biology to develop therapeutic regimens for metabolic diseases. Dr. Tagle said the vision would be to create a system of plug-and-play cassettes to generate biologics of interest, resulting in a novel catalog of genetic modules. In terms of possible obstacles, Dr. Tagle mentioned the lack of host diversity to generate synthetic products of interest, toxicity of desired products and naturally occurring mutations in hosts, and inadequate modeling of biosynthetic pathways based on rational design rules.

Dr. Tagle briefly summarized ongoing activity in this area. DARPA has a Living Foundries program for generating known materials on a small scale. NCATS' SBIR solicitations focused on small molecule natural products. The National Institute of Biomedical Imaging and Bioengineering runs the Synthetic Biology for Technology Development program. Finally, some limited efforts have attempted to use synthetic biology for therapeutics development.

Discussion

Dr. Ling recommended initiating this project, which could be an excellent opportunity to use the CAN Review Board's Other Transactional Authority. Careful management could lead to meaningful progress to help patients. He recommended establishing go/no-go parameters to drive progress. Nonperforming teams should be "fired." Also, scalability would be important to consider, and applicants should be required to show that they have robust systems. Dr. Ling also underscored the importance of taking posttranslational changes into account so the products would be ready for human testing. A further benefit would be that the project could lead to a disease-agnostic methodology. Dr. Ling speculated that some people may have *in silico* concepts worth considering.

Dr. Palkowitz thought this would be an excellent opportunity to anchor synthetic biology on a real problem. He suggested coupling the development of the molecular creations with evaluation measures, such as tissue penetration, bioavailability and immunogenicity. This approach would elucidate the properties and functions of macromolecules through structural and biophysical measures to understand how these systems relate to function. The project would not only have an impact on diseases but could also teach the community how to engineer large molecules for specific uses.

The members unanimously approved the START — Engineering Therapeutic Enzymes concept.

IX. NCATS TRIENNIAL INCLUSIONS REPORT: Valery M. Gordon, Ph.D., M.P.H., Senior Advisor for Human Subjects Protection, Division of Clinical Innovation, NCATS

Valery M. Gordon, Ph.D., M.P.H., said that this presentation grew out of the Public Health Service Act, which requires NIH to include women and minorities in NIH-funded research in a manner appropriate to the scientific questions under study. NIH reports aggregate data to Congress in the NIH Triennial Report. As part of the report, each NIH IC presents the data to its Advisory Council. Dr. Gordon further noted that the 21st Century Cures Act also requires data on the ages of participants.

According to Dr. Gordon, most of NCATS' support for research takes the form of partnerships with other NIH ICs to support the conduct of clinical research. To avoid duplication of reporting, the partnering IC — not NCATS — reports inclusion enrollment data. In her report, Dr. Gordon focused solely on NCATS programs for which NCATS enrollment data are collected, including CCIAs and SBIRawards.

Dr. Gordon presented demographic data from inclusion data records. Most of NCATS' research involves U.S. populations, and most NCATS studies enroll males and females. For single-sex studies, the majority have enrolled women only because of the scientific questions involved.

Dr. Gordon presented enrollment data by race/ethnicity and described plans to increase diversity in NCATS studies. In FY 2019, for example, NCATS will leverage the CTSA Program to improve health outcomes for rural, minority and special populations. Additionally, an NCATS workshop will address health disparities in vulnerable and underserved populations. In FY 2020, a new CTSA funding opportunity announcement will solicit proposals to develop and test clinical and translational solutions to health disparities.

Discussion

Dr. Hartman asked about the recruitment goals for minorities and women and whether NCATS is meeting those targets. Dr. Gordon acknowledged that the question was important, yet its answer is not straightforward. Many NCATS studies are small pilot-type studies. Also, enrollment needs to reflect the prevalence of the disease under study, and prevalence can vary by sex, age or race/ethnicity. However, when NCATS' data are compared with NIH-wide data, the distributions are similar. Dr. Hartman said that without any sort of targets, it is hard to understand whether the data are actionable.

Dr. Hartman discussed the idea of benchmarking the NCATS data against enrollment data from pharmaceutical company trials. The racial/ethnic diversity on NCATS studies probably would be comparable to industry trials. Dr. Gordon said that program staff must ensure that enrollment on NCATS studies is appropriate every year. Inadequate representation on trials is a basis for discontinuing funding. If an investigator is having trouble enrolling the right populations, program staff can assist. The CTSA Program's Recruitment Innovation Centers also can help investigators meet enrollment targets.

X. ADJOURNMENT OF THE OPEN MEETING

Dr. Austin thanked all participants for their input. He and Dr. Marks adjourned the open portion of the meeting at 2:55 p.m. ET.

XI. CLOSED SESSION OF THE NCATS ADVISORY COUNCIL

This portion of the Advisory Council meeting was closed to the public in accordance with the determination that it was concerned with matters exempt from mandatory disclosure under Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code, and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

Advisory Council members discussed procedures and policies regarding voting and the confidentiality of application materials, committee discussions and recommendations. Members did not participate in the discussion of and voting on applications from their own institutions or other applications in which there was a potential conflict of interest, real or apparent.

XII. ADJOURNMENT OF CLOSED SESSION OF THE NCATS ADVISORY COUNCIL MEETING

Dr. Austin adjourned the closed session of the NCATS Advisory Council meeting at 3:30 p.m. ET.

CERTIFICATION

We hereby certify that, to the best of our knowledge, the foregoing minutes and supplements are accurate and complete.

_____ _____

Christopher P. Austin, M.D. Date
Chair, NCATS Advisory Council;
and
Director, National Center for Advancing Translational Sciences, NIH

_____ _____

Anna L. Ramsey-Ewing, Ph.D. Date
Executive Secretary, Cures Acceleration Network Review Board;
and
Director, Office of Grants Management and Scientific Review, NCATS

_____ _____

G. Lynn Marks, M.D. Date
Chair, Cures Acceleration Network Review Board;
and
Senior R&D Advisor, Biomedical Advanced Research and Development Authority (BARDA), ASPR/HHS